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1 516 095

PATENT SPECIFICATION

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(54) 17,21-DIESTERS OF 17α,21-DIHYDROXY STEROIDS OF THE PREGNANE SERIES

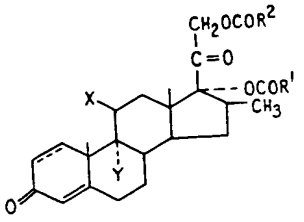
(71) We, GLAXO LABORATORIES LIMITED, a British Company of Greenford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel 17α,21 - diesters of 17α,21 - dihydroxy steroids of the pregnane series containing a basic 21 - ester grouping and having valuable anti-inflammatory activity.

It is known that certain 17α,21 - diesters of the pregnane series possess topical anti-inflammatory activity which in some cases, can be of a high order. In general, these steroids tend to be principally employed for the topical treatment of external inflammatory conditions. Also, these compounds generally possess substantially hydrophobic acyloxy ester groupings in the 17- and 21-positions and in the absence of any water-solubilising group these compounds cannot therefore be conveniently employed in aqueous preparations, e.g. for optic or ophthalmic use.

We have now discovered a new class of 17α,21 - diesters of the pregnane series having high systemic activity as well as good topical anti-inflammatory activity. The steroids moreover contain a water-solubilising or potentially water-solubilising ester grouping in the 21 - position.

These new steroids have a basic nitrogen-containing 21 - ester grouping and can be represented by the general formula



(I)

wherein X represents a β - hydroxy or keto group, Y represents a fluorine or chlorine atom, R^1 represents a hydrogen atom or an alkyl group containing 1—3 carbon atoms, R^2 represents a group of formula

$$-(CH_2)_nNR^3R^4$$

(wherein n is 1, 2 or 3 and R^3 and R^4, which may be the same or different, each represents an alkyl group containing 1—4 carbon atoms or R^3 and R^4 together with the adjacent nitrogen atom form a saturated substituted or unsubstituted monocyclic heterocyclic 4- to 7-membered ring, preferably 6-membered, which may further contain a sulphur or oxygen atom or another nitrogen atom) or R^2 represents a substituted or unsubstituted, nitrogen - containing, 6 - membered monocyclic heterocyclic ring attached to the adjacent carbonyl group via a carbon atom of the ring, and ⎯ ⎯ represents a single or double bond.

Where R^2 or NR^3R^4 represent a heterocyclic ring, this may if desired carry substituents, for example, C_{1-3} alkyl groups, e.g. methyl groups.

The compounds of formula I possess, as indicated above, both topical and systemic anti-inflammatory activity and are thus useful as general purpose anti-inflammatory agents. They are well absorbed on oral administration.

In addition, the marked skin thinning effect observed as an unwanted side-effect of certain widely used topical anti-inflammatory steroids is not observed with the compounds according to the invention in tests upon rats.

The above compounds also possess systemic immunosuppressive activity and are thus useful in the treatment of allergic disorders and inflammatory disorders having a significant immunological component. In experiments in rats it has been observed that the ratio of immunosuppressive to anti-inflammatory activity of the compounds according to this invention is greater than that of betamethasone.

In formula I above NR^3R^4 preferably represents a diethylamino group or an un-

substituted saturated 6 - membered heterocyclic ring, e.g. a piperidino or more preferably a morpholino group; n is advantageously 1. Alternatively, R^2 in formula I may advantageously represent an unsubstituted aromatic 6 - membered nitrogen - containing heterocyclic ring attached to the adjacent carbonyl group via a carbon atom, e.g. a pyridyl group, particularly the 3 - pyridyl group.

R^1 in formula I advantageously represents an alkyl group containing 1—3 carbon atoms, namely a methyl, ethyl, propyl or isopropyl group, an ethyl group, however, being preferred. In formula I, Y preferably represents a fluorine atom. X preferably represents a β - hydroxy group; $\overline{\overline{\overline{\ }}}$ preferably represents a double bond.

The present invention further includes acid addition salts of the above compounds of formula I particularly their hydrochlorides, hydrobromides, nitrates, phosphate, sulphates, p - toluene sulphonates, methanesulphonates, sulphosalicylates, maleates, fumarates, gluconates, citrates, tartrates, acetates, ascorbates, lactates and succinates. In order to attain aqueous solutions of acid addition salts of weakly basic compounds of formula I, such as those in which R^2 is morpholinomethyl, the pH of the solution is preferably adjusted to an acidic value.

The steroids according to the invention and their salts can generally be obtained as crystal forms containing water and/or other molecules of solvation.

An especially preferred compound of Formula I according to the invention by virtue of its particularly favourable anti-inflammatory activity is 9α - fluoro - 11β - hydroxy - 16β - methyl - 21 - morpholinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione. Other preferred compounds of formula I include

9α - fluoro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxy pregna - 1,4 - diene - 3,20 - dione;

21 - diethylaminoacetoxy - 9α - fluoro - 11β - hydroxy - 16β - methyl - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione;

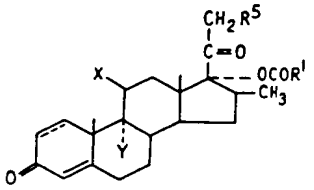
9α - fluoro - 11β - hydroxy - 16β - methyl - 21 - piperidinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione;

9α - chloro - 21 - diethylaminoacetoxy - 11β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione and

9α - chloro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione.

Further preferred compounds according to the invention are the acid addition salts, especially the hydrochlorides, of the above mentioned specific compounds of formula I.

The above compounds according to the present invention may be prepared for example, by reacting a compound of formula



(II)

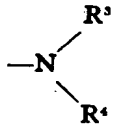
[wherein R^1, X, Y and $\overline{\overline{\overline{\ }}}$ are as hereinbefore defined and R^5 represents a hydroxy group or a group of formula

$$—OCO(CH_2)_nZ$$

(wherein n is as hereinbefore defined and Z represents a readily displaceable substituent)] with a compound of formula

$$H . R^6 \qquad III$$

[wherein R^6 represents a group of formula $OCOR^2$ (wherein R^2 is as defined above), or a reactive derivative thereof, when R^5 in formula II represents a hydroxy group; or R^6 represents a group of formula



(wherein R^3 and R^4 are as above defined) when R^5 in formula II represents a group of formula $—OCO(CH_2)_nZ$] or a functional equivalent thereof such as a corresponding acid addition salt.

When R_5 in formula II represents a hydroxy group, it is particularly preferred to use a reactive derivative of the compound of formula III in which R^6 represents a group $OCOR^2$ (wherein R^2 is as defined above), e.g. the corresponding acid anhydride or more preferably halide e.g. chloride or a functional equivalent thereof such as a corresponding acid addition salt.

The above-identified readily displaceable substituent Z may be for example a halogen atom, e.g. a bromine or iodine atom, or, more preferably, a chlorine atom, or an aromatic or aliphatic sulphonyloxy group, e.g. a p - toluenesulphonyloxy or methanesulphonyloxy group.

The reaction of the compounds of formulae II and III is preferably effected in a solvent medium, e.g. a ketone such as acetone or

methylethyl ketone; an acyclic ether such as diethyl ether or a cyclic ether such as tetrahydrofuran; an ester such as ethyl acetate; an amide solvent such as dimethylformamide or dimethylacetamide; or a halogenated hydrocarbon such as methylene chloride, advantageously at an elevated temperature, e.g. at the reflux temperature of the reaction mixture.

When R^5 in formula II above represents a haloacyloxy substituent or H . R^6 of formula III is in the form of an acid halide, the reaction is conveniently effected in the presence of an acid acceptor e.g. a tertiary organic base such as pyridine, collidine or triethylamine. When R^6 in formula III represents

$$—NR^3R^4,$$

the compound III can be used in excess to provide the above-mentioned said acceptor.

The acid addition salts of compounds of formula I may be prepared for example by treating the parent compound with an appropriate acid in water or an organic solvent medium, e.g. an alcohol such as ethanol or a hydrocarbon such as benzene.

The above-identified compounds of formula II wherein R^5 represents a group of formula

$$—OCO(CH_2)_nZ$$

may be readily prepared, for example, by reacting the parent 21 - hydroxy steroid with an appropriately substituted acylating agent, e.g. a halide or anhydride, e.g. a chloroacyl chloride or anhydride. This reaction is advantageously effected in a solvent medium, e.g. a solvent as mentioned above for the reaction of the compounds of formulae II and III.

The starting materials of formula II above wherein R^5 represents an iodoacyloxy group may, if desired, be prepared by reacting the corresponding compound of formula II wherein R^5 represents a chloroacyloxy group with a source of iodide ions, e.g. an iodide salt such as sodium iodide, the reaction being advantageously effected in a polar solvent medium such as a ketone solvent e.g. acetone or methylethylketone; an acyclic ether, e.g. diethyl ether or a cyclic ether, e.g. tetrahydrofuran; or an amide solvent such as dimethylacetamide or dimethylformamide.

The invention further comprises pharmaceutical compositions for human and veterinary practice comprising at least one compound of formula I (as herein before defined) or non-toxic acid addition salt thereof, together with one or more carriers or excipients with or without additional therapeutic agents.

Examples of compositions for topical administration include ointments, lotions, creams, powders and aerosol sprays; suppositories and retention enemas for the surface treatment of rectal areas; vaginal inserts; sterile drops and ointments for eye and ear treatment; slowly dissolving buccal pellets e.g. for the treatment of aphthous ulcers; chewing gum providing a slow release of the medicament for the treatment of the mucous membranes of the mouth and throat; nose and throat sprays and applications.

Antibacterial agents, such as antibiotics e.g. aureomycin, neomycin, or chemical agents, such as 8 - hydroxy - 7 - iodo - quinoline - 5 - sulphonic acid, may if desired be added to the steroid preparations detailed above for therapeutic advantage.

The proportion of active steroid in the topical compositions according to the invention will depend upon the precise nature of the formulation, but will generally be within the range of 0.0001%—5% by weight, advantageously 0.001%—0.5% by weight and preferably 0.01%—0.25% by weight.

The preparations may be administered once daily or more frequently dependent upon the nature of the condition being treated. Particularly beneficial results may be obtained in some cases by the use of occlusive dressings when the steroid is applied to the skin.

Veterinary preparations are, in general, formulated in analogous manner to those mentioned above, but with suitable adaption made for dose and size of the animals concerned. The steroid compound according to the invention may also be useful in intramammary preparations.

Compositions according to the invention also include compositions for the systemic absorption of the active compounds, for example, oral, rectal and parenteral compositions. Since the compounds according to the invention are highly potent, unit dosage forms are generally preferred. Convenient unit dosage forms for internal administration include tablets and capsules and these may, if desired, be formulated to give a sustained release of the active material. For parenteral use, convenient unit dosage forms include ampoules and vials, the latter being either single or multiple dose containers. Suppositories for systemic absorption may be prepared, for example using a convenient suppository base in conjunction with a suitable carrier to aid absorption from the colon.

Compositions according to the invention for internal administration may also include additional active ingredients such as antibacterial agents, e.g. neomycin. Compositions for parenteral administration may also be prepared as sterile dry solids for reconstitution with a sterile diluent, immediately before use.

Preparations for systemic use in unit dosage form may contain from 0.05 to 10.0 mg, pre-

ferably 0.50 to 5.0 mg, of the active steroid per unit dosage. Generally the preparations for internal administration may contain from 0.01 to 50% of active ingredient, dependent on the type of preparation involved. In veterinary preparations, dosages vary considerably depending on the size of the animal and the frequency of administration of the composition.

The following Examples illustrate the invention. Unless otherwise stated optical rotations were measured in dioxan at *ca* 1% concentration. Ultraviolet spectra were measured in ethanol. Organic extracts were dried over magnesium sulphate or sodium sulphate. Temperatures are in degrees Centigrade.

Example 1

9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - morpholinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione

(i) A solution of crude betamethasone 17 - propionate 21 - chloroacetate (8.3 g) and morpholine (6.9 ml) in anhydrous acetone (275 ml) was refluxed for 1 hour. The mixture was evaporated to give a yellow oil, which was dissolved in ethyl acetate (350 ml) and extracted with water (2×350 ml). The dried organic phase was evaporated to a yellow oil, which was crystallised from ethanol to give the *title compound* as a white powder (7.5 g), m.p. 124—125°. An analytical specimen, as a monohydrate (from ethanol), had m.p. 128—130°; $[\alpha]_D$+62°, λ_{max} 237 nm (ε 15,630).

(ii) A solution of betamethasone 17 - propionate 21 - iodoacetate (1.8 g.) and morpholine (.27 ml.) in acetone (AR, 80 ml.) was refluxed for 1½ hours. The mixture was cooled and evaporated in vacuo to a yellow gum which was partitioned between ethyl acetate and water, the mixture being adjusted to pH 7 with N - hydrochloric acid. The aqueous phase was extracted further with ethyl acetate and the combined organic extracts were washed with water, dried and evaporated under reduced pressure to an off-white foam (1.86 g.). Crystallisation and recrystallisation from aqueous methanol gave colourless crystals (1.0 g.) of the *title compound*, as a monohydrate, m.p. 122—125°, $[\alpha]_D$+62°, λ_{max} 236.5 nm (ε 16,000).

Example 2

9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - morpholinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione hydrochloride

(i) A solution of betamethasone 17 - propionate 21 - morpholinoacetate (2 g) in anhydrous ethanol (5 ml) was treated with 0.6 *N* HCl in ethanol (6 ml), left for 15 minutes at room temperature in a well stoppered conical flask and evaporated to give an almost colourless oil. After drying the oil *in vacuo* at 50° for 3 hours, the residual glassy material was dissolved in the minimum amount of acetone and stored at 5° for 3 hours. The product was collected and dried *in vacuo* at 50° for 3 hours to give white crystals of the *title compound* (1.85 g). An analytical specimen (from acetone) in the form of an acetone solvate had m.p. near 70°; $[\alpha]_D$+95° (dilute hydrochloric acid); λ_{max} 238 nm (ε 15,300).

(ii) A sample (2.00 g.) of betamethasone 17 - propionate 21 - morpholinoacetate hydrochloride prepared as in (i) above shown, by p.m.r. spectroscopy, to be solvated with acetone [*ca.* 0.5 mole] was dissolved in warm methanol and the solution was filtered, then evaporated to a smaller volume by boiling. Ethyl acetate was added gradually and crystallisation was induced to give colourless crystals (1.75 g.). Further recrystallisation carried out in a similar manner gave, after drying overnight at 50°/0.1 mm, colourless crystals (1.48 g.) of the *title compound*, as a hemihydrate, m.p. 175—180°, $[\alpha]_D$+93° (*ca.* 0.1 *N* - hydrochloric acid), $[\alpha]_D$+81.5° (dioxan), λ_{max} 239 nm (ε 15,500). The infrared spectrum (in Nujol—registered Trade Mark) different from that of the starting sample in the same medium, and the p.m.r. spectrum (in deuteriochloroform) did not reveal solvation by methanol, ethyl aceate or acetone.

Example 3

9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione

Betamethasone 17 - propionate (1 g.) in dry pyridine (17 ml.) was treated with nicotinyl chloride hydrochloride (1 g.) at room temperature for 80 minutes and then at 0° for 16 hours. Dilution with water gave a crude product which was dissolved in benzene, cooled in ice and treated with hydrogen chloride to give an oil. The solvent and excess hydrogen chloride were removed *in vacuo*. More benzene was added and again removed *in vacuo*. The process was repeated once more and then water was added and the mixture stirred and filtered. The insoluble solid was again dissolved in benzene (20 ml.) and a solution of hydrogen chloride (250 mg.) in benzene (15 ml.) added. The solid was filtered off and partitioned between chloroform and dilute ammonia. The organic layer was washed, dried and evaporated to give a froth 810 mg.). A portion (300 mg.) was purified by preparative thin layer chromatography [silica; developing 6 times with chloroform: acetone (6:1)] to give material which crystallised from methanol. Recrystallisation from methanol afforded the *title compound*, hydrated with half a molecule of water, as fine needles, m.p. 138—139° $[\alpha]_D$+113.4°.

Example 4

21 - Diethylaminoacetoxy - 9α - fluoro - 11β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione hydrochloride

Betamethasone 17 - propionate 21 - chloroacetate (1.9 g.) in acetone (100 ml.) was treated with dry sodium iodide (2 g.) and the mixture refluxed for 2 hours. Dilution with water afforded crude 21 - *iodoacetate* which was dried, dissolved in acetone (80 ml.) and refluxed with diethylamine (1.2 ml.) for 1.5 hours. Evaporation of the solvent gave a dark red-brown solid which was filtered through Florosil (registered Trade Mark) (70 g.) in ethyl acetate. The material eluted with ethyl acetate was dissolved in benzene and treated at 0° with hydrogen chloride. The solvent and excess hydrogen chloride were removed *in vacuo* and the residue partitioned between water and ether. The aqueous layer was freeze dried to yield the *title compound* hydrated with two molecules of water, (1.13 g.) as an amorphous solid, $[\alpha]+84.4°$ (H_2O), $\lambda_{max.}$ 237—239 nm (ϵ 14,800).

Example 5

9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - piperidinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione hydrochloride

A mixture of betamethasone 17 - propionate 21 - iodoacetate (1.8 g.) and redistilled piperidine (1.44 ml.) in acetone (80 ml.) was refluxed for *ca.* 1½ hours then evaporated *in vacuo* at room temperature. The residue was partitioned between a mixture of benzene (100 ml.), ether (50 ml.), ethyl acetate (50 ml) and *ca* 0.5 N hydrochloric acid (600 ml.), then the aqueous phase was washed with benzene (2×50 ml) then stirred with chloroform (50 ml.) and basified to pH 8.0 with ammonia. The aqueous phase was further extracted with chloroform (3×100 ml.) and the combined extracts were washed with water (20 ml.), decolourised (charcoal), dried and evaporated *in vacuo;* the residual foam was triturated with petrol to give the *21 - piperidinoacetate* (1.68 g) as a pale brown solid, $\lambda_{max.}$ 237 nm (ϵ 15,200).

A solution of the crude free base (1.43 g) in benzene (50 ml.) was cooled to 0° and treated with dry hydrogen chloride for *ca* 30 seconds. Volatile material was removed *in vacuo* at room temperature, replaced with fresh benzene and the evaporation was repeated; the residual material was partitioned between water and ether and the aqueous phase freeze dried to give the hydrochloride as a solid (940 mg.) which crystallised from acetone as colourless needles (799 mg.), m.p. 165—167.5°; concentration of mother liquors gave a second crop (23 mg) m.p. 66.5—167.5°. Recrystallization of the two crops from acetone gave the analytical sample of the *title* compound, hydrated with half a molecule of water, as colourless hygroscopic needles (688 mg.), m.p. 167.5—169.5°, $[\alpha]_D+80°$ (very dilute hydrochloric acid), $\lambda_{max.}$ 238 nm (ϵ 15,700).

Example 6

9α - Chloro - 21 - diethylaminoacetoxy - 11β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione hydrochloride

A solution of 9α - chloro - 21 - chloroacetoxy - 11β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione (.7 g.) in acetone (80 ml.) was treated with sodium iodide (1.7 g.) and the solution refluxed for 4 hours. The mixture was poured into water (2 l.) and the precipitated material washed and dried to give the *21 - iodoacetate* (1.9 g.).

The above iodo-acetate (1.75 g.) in acetone (70 ml). was treated with diethylamine (0.88 ml.) and the mixture refluxed for 1½ hours. The acetone was removed *in vacuo* and water (35 ml.) added. The aqueous mixture was extracted with chloroform to give the *21 - diethylaminoacetate* as a froth (1.6 g.). This material, in benzene solution, was treated at room temperature with a solution of hydrogen chloride (106 ml.) in benzene (14.5 ml.). The benzene was evaporated *in vacuo* and the residue partitioned between water and ether. The aqueous solution was freeze dried to give the *title compound* (1.41 g.) as an off white amorphous solid. A portion was purified further by taking it up in water, extracting with ether, heating the aqueous solution of the steam bath with charcoal, filtering and freeze drying the resulting solution, to give the *title compound* as a white amorphous solid solvated with 2.5 molecules of water, $[\alpha]_D+92.1°$ (H_2O).

Example 7

9α - Chloro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione

9α - Chloro - 11β,21 - dihydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione (1 g.) and nicotinyl chloride hydrochloride (1 g.) were dissolved in dry pyridine (17 ml.) and stood at room temperature for 3 hours. The mixture was then poured into water and the precipitated solid was filtered off and dried. Recrystallisation from methanol gave the *title compound* as a monohydrate, (924 mg.), m.p. 150° (capillary), $[\alpha]_D+129.6°$, λ inflexion 237—239 nm (ϵ *ca.* 19,600).

Example 8

9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - morpholinoacetoxy - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione.

A mixture of 4 - morpholinoacetic acid (1.439 g, prepared by the method of A. L. Remizov and N. V. Khromov-Borisov, Zhur. Obshchei Khim., 1953, 23, 794; Chem. Abs. 1954, *48*, 3908e.) and thionyl chloride (5.3 ml.) was stirred at room temperature for 18½ hours with exclusion of atmospheric moisture. Volatile material was removed by evaporation at room temperature for one hour and the residual solid was suspended in dry tetrahydrofuran (10 ml). This was then added to a well stirred suspension of betamethasone 17 - propionate (1.01 g.) in dry tetrahydrofuran (10 ml.) containing pyridine (0.31 ml) and stirring was continued at room temperature for 3½ hours. Solvent was removed under reduced pressure and the residue was partitioned between water (200 ml.) and ethyl acetate (200 ml.) then adjusted to pH 7 with saturated sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (100 ml.): the combined organic phases were washed with water, dried (magnesium sulphate) and solvent was evaporated to give a pale yellow foam (1.158 g.). The foam was partitioned between ethyl acetate (50 ml.) and 2N - hydrochloric acid (50 ml). and the organic phase was extracted with more acid (20 ml.): the combined acidic aqueous extracts were washed with ethyl acetate (30 ml.) then adjusted to pH 7 with 2N - sodium carbonate solution whilst being stirred under ethyl acetate (50 ml.). The aqueous phase was separated and extracted further with ethyl acetate; the combined ethyl acetate extracts were washed with water, dried (magnesium sulphate) and evaporated to an off-white foam (441 mg.). This was crystallised and recrystallised from aqueous methanol to give the title 21 - morpholinoacetate as colourless crystals (360 mg.), m.p. 122—125°C (Kofler), $[\alpha]_D$+59.3° (c 1.03, dioxan), λ_{max} (ethanol) 237.5 nm ($E_{1\,cm}^{1\%}$ 269), which were almost homogeneous, the major component being identical with an authentic specimen on thin-layer chromatography (silica, chloroform - acetone 2:1, and benzene - acetone 1:1).

Preparation 1

9α - Chloro - 11β,21 - dihydroxy - 16β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione

9α - Chloro - 11β,21 - dihydroxy - 16β - methyl - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione (2 g.) in dry tetrahydrofuran (60 ml.) was treated with pyridine (1.5 ml.) and chloroacetic anhydride (1.5 g.). The mixture was stood at room temperature for 2 hours and then poured into dilute hydrochloric acid (2 l.). The precipitated solid (2.34 g) was filtered off, washed and dried, and a portion (640 mg.) was recrystallised from acetone - petroleum ether to give the *title compound* (484 mg.), m.p. 168—170° (capillary), $[\alpha]_D$+86.8°, (c 1.37%), λ_{max}. 238 nm (ε 13,780).

Preparation 2

Betamethasone 21 - chloroacetate 17 - propionate

Betamethasone 17 - propionate (8.97 g.) in dried and distilled tetrahydrofuran (270 ml.) was stirred and treated with chloroacetic anhydride (4.1 g), followed by dry pyridine (1.57 ml.); stirring was continued for 2 hours at room temperature. Water (50 ml) was added and the mixture was evaporated at 40°. The residue (oil) was dissolved in ethyl acetate (500 ml.) and extracted first with a mixture of 2 *N* hydrochloric acid (30 ml.) and water (270 ml); then with 10% aqueous sodium hydrogen carbonate (100 ml) and finally with water (500 ml.) until the pH of the washings was neutral. The organic phase was dried and evaporated at 40°. The residue (oil) was dissolved in ethanol (100 ml.) at 60° and evaporated to about ½ volume. On cooling a white product began to separate, which was collected and dried *in vacuo* to give the *title compound* (9.0 g.) m.p. 180—185°.

Preparation 3

Betamethasone 21 - iodoacetate 17 - propionate

Crude betamethasone 17 - propionate 21 - chloroacetate (4.5 g.) and dry sodium iodide (4.8 g.) in acetone (230 ml.) were refluxed for 3 hours. After being cooled the reaction mixture was poured into water (600 ml.) to give, after prolonged stirring, a colourless solid (4.26 g.). A portion (194 mg.) was recrystallised twice from methanol to give the *title compound* as colourless crystals (122 mg.), m.p. 180—182°, $[\alpha]_D$+46°, $\lambda_{max.}$ 238 nm (ε 16,100).

The following Examples illustrate pharmaceutical compositions according to the invention:

Example A

Water-miscible cream

Active ingredient (free base)	0.1% w/w
Beeswax	15.0%
Glycerol	15.0%
Polyoxyethylene 25 lanolin derivative	2.0%
Methyl paraben	0.08%
Propyl paraben	0.2%
Sodium citrate B.P.	0.15%
Citric acid	qs. to pH 6.5—7.5
Water to	100.00%

Melt together the beeswax and polyoxyethylene 25 lanolin derivative and heat to 75°C. Mix some or all of the glycerol with some or

all of the wa
the parabens
aqueous solut
Stir with co
either dissolv
remaining wa
with stirring
in the remain
tant suspensio
sufficient citr
6.5—7.5, and

Oral tablet

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base)
Lactose
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WHAT WE
1. Compour

wherein X rep

all of the water and heat to 75°C. Dissolve the parabens and sodium citrate in the aqueous solution and mix the two phases. Stir with cooling to 50—60°C and then *either* dissolve the active ingredient in the remaining water and add this to the base with stirring *or* ball-mill the active ingredient in the remaining glycerol and add the resultant suspension to the base with stirring. Add sufficient citric acid to adjust the pH to 6.5—7.5, and continue stirring until cool.

Example B

Oral tablet

Active ingredient (free base)	0.5 mg.
Lactose	175.5 mg.
Maize starch (dried)	20.0 mg.
Gelatin	2.0 mg.
Magnesium stearate	2.0 mg.
Tween (registered Trade Mark) 80	Trace
Total weight	200.0 mg.

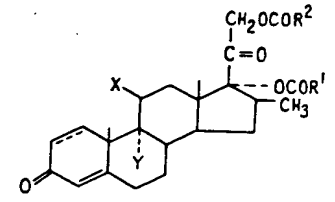
A suspension of 300 mg. of the active ingredient in 2 ml. of water containing 0.1% of Tween 80 is milled for 16 hours in a 10 ml. nylon pot about three quarters filled with steatite balls, until 90% by number of the particles have a diameter of less than 5 microns with none greater than 50 microns. The maize starch and lactose are blended and passed through a 60 mesh B.S. sieve and granulated with a solution of gelatin, containing the suspension of the active ingredient and washings from the nylon pot, by passing through a 16 mesh B.S. sieve. The granules are dried at 40°C overnight, passed through a 20 mesh B.S. sieve and blended with magnesium stearate and tabletted using a tabletting machine having a 5/16 inch flat-bevelled punch.

The active ingredient may alternatively be used in the form of a salt, in which case the quantity used will be that containing 0.5 mg. free base, the quantity of lactose being correspondingly reduced.

Where the active ingredient dissolves in the water component, the ball milling stage may be omitted.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



(I)

wherein X represents a β - hydroxy or keto group, Y represents a fluorine or chlorine atom, R^1 represents a hydrogen atom or an alkyl group containing 1—3 carbon atoms, R^2 represents a group of formula

$$-(CH_2)_nNR^3R^4$$

(wherein n is 1, 2 or 3 and R^3 and R^4, which may be the same or different, each represents an alkyl group containing 1—4 carbon atoms or R^3 and R^4 together with the adjacent nitrogen atom form a saturated substituted or unsubstituted monocyclic 4 to 7 membered, heterocyclic ring, which may further contain a sulphur or oxygen atom or another nitrogen atom) or R^2 represents a substituted or unsubstituted monocyclic, 6 - membered nitrogen-containing heterocyclic ring attached to the adjacent carbonyl group via a carbon atom of the ring, and ═══ represents a single or double bond.

2. Compounds as claimed in Claim 1 wherein R^3 and R^4 together with the adjacent nitrogen atom form a 6-membered heterocyclic ring.

3. Compounds as claimed in Claim 1 wherein R^3 and R^4 together with the adjacent nitrogen atom form an unsubstituted 6 - membered heterocyclic ring.

4. Compounds as claimed in Claim 3 wherein R^3 and R^4 together with the adjacent nitrogen atom form a morpholino group.

5. Compounds as claimed in Claim 3 wherein R^3 and R^4 together with the adjacent nitrogen atom form a piperidino group.

6. Compounds as claimed in Claim 1 wherein R^3 and R^4 each represent an ethyl group.

7. Compounds as claimed in any of the preceding Claims wherein R^2 represents a group of formula

$$-(CH_2)_nNR^3R^4$$

in which n is 1.

8. Compounds as claimed in Claim 1 wherein R^2 or NR^3R^4 represents a heterocyclic ring substituted by one or more C_{1-3} alkyl groups.

9. Compounds as claimed in Claim 1 wherein R^2 represents an unsubstituted aromatic 6 - membered nitrogen - containing heterocyclic ring attached to the adjacent carbonyl group via a carbon atom of the ring.

10. Compounds as claimed in Claim 9 wherein R^2 represents a pyridyl group.

11. Compounds as claimed in Claim 10 wherein R^2 represents a 3 - pyridyl group.

12. Compounds as claimed in any of the preceding Claims wherein R^1 represents an alkyl group containing 1 to 3 carbon atoms.

13. Compounds as claimed in Claim 12 wherein R^1 represents an ethyl group.

14. Compounds as claimed in any of the

preceding claims wherein Y represents a fluorine atom.

15. Compounds as claimed in any of the preceding claims wherein X represents a β-hydroxy group.

16. Compounds as claimed in any of the preceding claims wherein ═══ represents a double bond.

17. 9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - morpholinoacetoxy - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione.

18. 9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione.

19. 21 - Diethylaminoacetoxy - 9α - fluoro - 11β - hydroxy - 16β - methyl - 17 - propionyloxy - pregna - 1,4 - diene - 3,20 - dione.

20. 9α - Fluoro - 11β - hydroxy - 16β - methyl - 21 - piperidinoacetoxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione.

21. 9α - Chloro - 21 - diethylaminoacetoxy - 11β - hydroxy - 16β - methyl - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione.

22. 9α - Chloro - 11β - hydroxy - 16β - methyl - 21 - nicotinyloxy - 17 - propionyloxypregna - 1,4 - diene - 3,20 - dione.

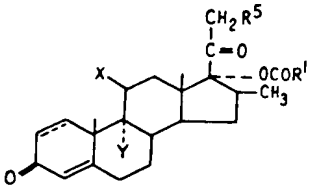
23. Compounds as claimed in any of the preceding Claims in the form of their acid addition salts.

24. Compounds as claimed in any of Claims 1 to 22 in the form of their hydrochlorides.

25. Compounds as claimed in any of Claims 1 to 22 in the form of their hydrobromides, nitrates, phosphates, sulphates, p - toluene - sulphonates, methane - sulphonates, sulphosalicylates, maleates, fumarates, gluconates, citrates, tartrates, acetates, ascorbates, lactates or succinates.

26. Compounds as claimed in any of the preceding Claims in the form of a solvate thereof.

27. A process for the preparation of compounds of formula I (as defined in Claim 1) which comprises reacting a compound of formula



II

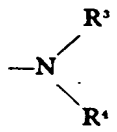
[wherein R^1, X, Y and ═══ are as defined in Claim 1 and R^5 represents a hydroxy group or a group of formula

$$—OCO(CH_2)_nZ$$

(wherein n is as defined in Claim 1 and Z represents a readily displaceable substituent)] with a compound of formula

$$H . R^6 \qquad III$$

[wherein R^6 represents a group of formula $OCOR^2$ (wherein R^2 is as defined in Claim 1) or a reactive derivative thereof when R^5 in formula II represents a hydroxy group; or R^6 represents a group of formula



(wherein R^3 and R^4 are as defined in Claim 1) when R^5 in formula II represents a group of formula $—OCO(CH_2)_nZ$ (wherein n and Z are as above defined]) or a functional equivalent thereof.

28. A process as claimed in Claim 27 wherein a compound of formula II (wherein R^5 represents a hydroxy group) is reacted with a reactive derivative of the compound of formula III [wherein R^6 represents a group of formula $—OCOR^2$ (in which R^2 is as defined in Claim 27)].

29. A process as claimed in Claim 27 or Claim 28 wherein the said reactive derivative of the compound of formula III is an acid halide or anhydride.

30. A process as claimed in Claim 29 wherein the said reactive derivative of the compound of formula III is an acid chloride.

31. A process as claimed in any of Claims 27 to 30 wherein the compound of formula III is in the form of an acid addition salt thereof.

32. A process as claimed in Claim 27 wherein R^5 in formula II represents a group of formula $—OCO(CH_2)_nZ$ in which Z represents a halogen atom or an aromatic or aliphatic sulphonyloxy group.

33. A process as claimed in Claim 32 wherein Z represents a bromine, iodine or chlorine atom or a p - toluenesulphonyloxy or methanesulphonyloxy group.

34. A process as claimed in any of Claims 27 to 33 wherein the reaction is effected in the presence of an acid acceptor when R^5 in formula II represents a group of formula

$$—OCO(CH_2)_nZ$$

(in which Z represents a halogen atom) or when the compound of formula III (in which R^6 represents a group of formula $—OCOR^2$) is employed in the form of an acid halide.

35. A process for the preparation of addition salts of compounds of formula I (as defined in Claim 1) which comprises treating

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the parent compound of formula I with an appropriate acid.

36. A process for the preparation of compounds of formula I (as defined in Claim 1) and their acid addition salts substantially as herein described.

37. A process for the preparation of compounds of formula I (as defined in Claim 1) and their acid addition salts substantially as herein described with reference to any of Examples 1 to 7.

38. Compounds of formula I (as defined in Claim 1) and their acid addition salts whenever prepared by a process as claimed in any of Claims 27 to 37.

39. Pharmaceutical and veterinary compositions comprising, an active ingredient, at least one compound of formula I (as defined in Claim 1) and/or non-toxic acid addition salt thereof, together with one or more carriers or excipients.

40. Compositions as claimed in Claim 39 adapted for topical administration.

41. Compositions as claimed in Claim 40 in the form of ointments; lotions; creams; powders; aerosol sprays; suppositories and retention enemas for topical administration; vaginal inserts; drops; pellets; chewing gums; or nose and throat sprays and applications.

42. Compositions as claimed in Claim 39 adapted for oral, rectal or parenteral administration.

43. Compositions as claimed in Claim 42 in dosage unit form.

44. Compositions as claimed in Claim 43 in the form of tablets, capsules, ampoules, vials or suppositories.

45. Compositions as claimed in Claim 44 containing 0.05 to 10.0 mg of active ingredient per dosage unit.

46. Compositions as claimed in Claim 45 containing 0.50 to 5.0 mg. of active ingredient per dosage unit.

47. Pharmaceutical or veterinary compositions according to claim 39 substantially as herein described.

48. Pharmaceutical or veterinary compositions substantially as herein described with reference to either of Examples A and B.

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